

Supplemental Material

Ethical Issues in measuring biomarkers in children's environmental health.

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Ethical Aspects of Research Involving Children

Statements on the ethical conduct of research issued by various national and professional bodies generally include a section outlining the special requirements for including children in research (Meslin and Johnson 2008; 1993; 1998; 2000; 2007). Common to all of these guidelines are three general protections: sound justification; informed consent and prior ethics review.

Sound justification. These protections make the ethical presumption that these groups should not be included in research unless there is a compelling reason to do so. Ironically, the laudable desire to protect the vulnerable from research risk also meant that little research could be conducted leading to a situation in which any health benefits would be slow in coming. In an attempt to address this a major shift occurred in U.S. regulatory policy occurred in 1993: rather than excluding women and children from research, the NIH made clear its commitment to requiring that women be included in trials unless there was a reason not to in the 1994 *NIH Reauthorization Act*.

Research specifically involving children is only considered to be ethically justifiable (1998; Boddington and Hogben 2006; Gandhi 2005; Kanner et al. 2004; Merlo et al. 2007; Neill 2005; O'Lonergan and Milgrom 2005; Ross 2003; Sauer and Ethics Working Group 2002) where:

- a. The research question is important to the health and well being of children;
- b. The participation of children is essential because only research in children can adequately answer the question;

- c. The study methodology is appropriate for children of the age range included in the study, i.e. the methodology is developmentally-appropriate;
- d. The circumstances in which the research is conducted adequately provide for the physical, emotional and psychological safety of the child.

Informed Consent.

The basis for this assessment is sometimes found in the bioethical principle of respect for persons described in *Belmont* (1979) or respect for autonomy (Beauchamp and Childress 2005). Both principles understand that only adults are presumed to have the capacity to act autonomously, whereas children are not presumed to have this capacity. In general, consent is given on their behalf by parents or legal guardians, usually supplemented by the positive affirmation (or assent) of the child where possible (De Lourdes Levy et al. 2003).

Other principles are invoked in support of pediatric research. For example, the ethical principle of justice includes the concept that children and the societies in which they live are likely to be disadvantaged if children are not included in research. This principle is well demonstrated in the area of medications, where children are frequently treated with drugs that have never been tested or shown to be safe for children (Holt et al. 2004). Indeed, the concept of protecting vulnerable groups, including children, “from” research has translated into excluding these groups from clinical research in some circumstances (Park and Grayson 2008). In discussing this concept, Park and Grayson (Park and Grayson 2008) suggest that the concept of “vulnerability” in research is largely based on a lack of ability to provide informed consent; children fall under this definition. However,

they propose that under some circumstances ethics review boards should take into consideration the value of the research question; the value of the information to be gained from the research to the study population or to the society as a whole may override the inability to obtain informed consent from all participants (Park and Grayson 2008). This concept has been included in the most recent Australian guidelines (2007) for some epidemiology research.

Since informed consent is tightly connected to assessment of risk and benefit, consideration is also given to the nature of risk involved in research. The greater the risk, the more comprehensive the consent should be. For example, U.S. regulations for children distinguish four types of research:

- (1) Research not involving greater than minimal risk,
- (2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects,
- (3) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, and
- (4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (See 45 CFR 46, Subpart D. Subsections 404, 405, 406, 407.

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>). Because more or less protections may hinge on the determination of which category of risk into which a study may fall, discussion continues as to how such judgments should be made. (Seema et al,

2004). Although the regulatory requirements may differ in different countries, the principles underlying them may apply equally to biomarker research in children.

Case Study: Children's Environmental Exposure Research Study (CHEERS)

Funders: EPA, CDC, Duval County Health Department, and the American Chemistry Council, under a Cooperative Research and Development Agreement (CRADA) with EPA

Aims: The CHEERS study is designed to fill critical data gaps regarding children's exposure to pesticides and other chemicals in the home environment. The research questions are:

- (1) To gain a better understanding of how children are exposed to pesticides and other chemicals found in homes and the factors that affect their exposure
- (2) To understand how children's ages and activities affect their exposure at home.
- (3) Ensure rigorous scientific and ethical standards are used throughout the study
- (4) To use the data generated to improve risk assessments and to develop risk mitigation strategies

Population:

3.1.1 General Information and Demographics of Duval County and Jacksonville, FL

Duval County, FL, which includes the Jacksonville metropolitan statistical area (MSA), has a land area of 774 square miles. The County, with a population of 778,879 in the 2000 Census, includes the city of Jacksonville (population of 735,617), Atlantic Beach (13,368), Baldwin (1,634), Jacksonville Beach (20,990), and Neptune Beach (7,270). The population density is 1,006 persons per square mile. The 2000 Census reported 303,747 households in the County, of which 37% were with persons under 18. Median household income in the county was \$35,883 compared to \$32,877 for the state of Florida (model-based estimates) in 1997. The proportion of children living below the poverty level in Duval County in 1997 was estimated to be 18.8%, which is slightly lower than the figure of 21.8% estimated for the entire state. Duval County and the city of Jacksonville operate under a consolidated government. The population of the county is diverse, as shown in Table 3-1. Table 3-1 also shows that there are approximately 11,500 births in the County each year (i.e., approximately 1000 births per month), a number that should be sufficient for effective recruiting of children into the study.

Design: CHEERS is a field monitoring study designed to evaluate the exposure of young children to pesticides and other chemicals as a result of normal use in their homes. This longitudinal field measurement study includes either five or six repeat visits to the same participating families over a two year period. Each monitoring visit will last for five days, during which samples will be collected on a daily basis. Sixty young children will be enrolled in two cohorts:

- (1) children who are approximately 12 months of age at the time of enrollment
- (2) children who are less than 3 months of age at the time of enrollment

Environmental, biological, personal, activity pattern, and questionnaire data will be collected.

- Pesticide use information (application method, active ingredient, amount of active ingredient, area treated, number of applications per year, total amount of active ingredient applied per year, interval between applications, and day of week use).
- Pre- and post-application pesticide concentrations in all relevant media in both treated and untreated rooms.
- Post-application decay profiles.
- Transfer coefficients, with estimates of intra- and inter-child variability and the influence of age, sex, activity level, surface-type, and season.
- Macroactivities (time spent in treated and untreated rooms, active play, quiet play, sleeping, and eating) with estimates of intra- and inter-child, day-of-week, and seasonal variabilities.
- Frequency of hand washing and bathing events.
- Dietary information (food and beverages).

Eligibility Criteria:

3.2.1 Eligibility Criteria

To meet the objectives of the study, it is critical that a high proportion of both environmental and biological samples have measurable levels of pesticides. A high frequency of detection is important, for example, to evaluate the factors that affect exposure. Therefore, the study will be performed in residences expected to have high pesticide use based on pesticide frequency and patterns of use as reported by the participants and results of a screening visit to the potential participant's home. It should be recognized that it is difficult to define high pesticide use for either the general population or the population targeted for inclusion in this study. There are few data that can be used for that purpose. However, the data from the study performed by EPA/CDC/DCHD in Jacksonville in the summer of 2001 will be available prior to recruiting and will be analyzed to develop an initial definition of high pesticide use for the study participants. Criteria for eligibility in the study will include the following:

- Age of the child at time of recruitment: newborn or one-year old,
- High pesticide use in the residence,
- Participant child will not attend day care outside of the home,
- Participant lives in a permanent residence (not transient housing),
- Participant is willing to advise field measurement team of planned pesticide applications,
- Participant will collect urine samples and diet samples, and,
- Participant is willing to participate in the study for two years.

In addition, a limited number of individuals (less than 10% of the total participants) will be recruited who are known to have very low pesticide usage. This group will serve as the study comparison group.

Compensation:

Activities	Amount	Remarks
Screening visit to determine eligibility	\$ 20.00	
First event for the cohort	\$ 100.00	Prepay \$25 during pre-application visit
Second event for the cohort	\$ 100.00	Prepay \$25 during pre-application visit
Third event for the cohort	\$ 150.00	Prepay \$25 during pre-application visit
Fourth event for the cohort	\$ 150.00	Prepay \$25 during pre-application visit
Fifth event for the cohort	\$ 200.00	Prepay \$25 during pre-application visit
Sixth event for the cohort	\$ 200.00	* Cohort 2 only
1 Blood sample – adult	\$ 25.00	
1 Blood sample – child	\$ 25.00	
Total Cohort 1	\$ 770.00	If all study activities are completed
Total Cohort 2	\$ 970.00	If all study activities are completed

Supplemental Material, Table 1

Discussion questions

1. What ethical issues, if any, would you raise if you were a high level scientist at the EPA reviewing this study?
2. What ethical issues, if any, would you raise if you were a community member in Duval County?
3. Given that we do not know the health effects of low-level, chronic pesticide exposure, would it have been appropriate to include an intervention in the study? Would you feel differently about the study if there was an intervention?

Case Study: Lead Abatement and Repair and Maintenance Study

Funders: EPA's Office of Pollution Prevention and Toxics and HUD's Office of Lead Hazard Control

Aims: In the late 1980's and early 1990's when the study was being conceived, 95% of the housing in Baltimore's low-income, high risk neighborhoods was filled with lead. The best known solution to this problem, lead abatement, was more costly than the homes themselves. The Kennedy Krieger Institute (KKI), a non-profit institute affiliated with Johns Hopkins dedicated to the treatment of children with developmental diseases and disabilities, designed a study to determine effective, lower cost alternatives to reduce lead levels in homes. Identifying lower cost methods of lead abatement was important in Baltimore because landlords would abandon buildings if they had to pay for expensive lead abatement and the city was in need of preserving affordable housing.

Design: The study was designed to characterize and compare the short-term (six months) and longer term (up to 24 months) efficacy of the lead abatement methods which KKI had proved to be effective in reducing children's exposure to residential paint and dust, and thereby reducing children's risk of lead poisoning.

There were five groups of homes in the study. The first three groups had interventions that varied by the amount spent on repair and maintenance.

(1) Level I: Minimal repair and maintenance (\$1,650)

- (2) Level II: Greater amount of repair and maintenance (\$3,500)
- (3) Level III: Greater amount of repair and maintenance (\$6,500)
- (4) Level IV: “Every known intervention to make these homes as safe as possible”
(this group of homes was abated by the City of Baltimore before the study began)
- (5) Homes in this group were built after 1978 when lead paint was forbidden in homes.

The study called for follow-up by KKI researchers if there was an increase of 5 or more micrograms per deciliter in blood lead levels or if a blood lead level reached 20+ micrograms per deciliter.

Population: The population involved in this study included children of families in the homes included in the study. The study included approximately 75 structurally sound homes in high-risk neighborhoods in Baltimore that had not previously received lead reduction improvements. KKI staff interviewed families in the identified homes to see if they met the study’s inclusion criteria (absence of certain health issues and the presence of one or more young children). If a family agreed to participate the landlord could apply for the State Loan Program for lead reduction, which paid for the repairs. Some of the homes that were included in the study were not occupied at the beginning. Families who moved into participating homes after lead reduction repairs were conducted were invited to participate at that time.

The specifics of the housing occupation was as follows (from Pollak J. Journal of Health Care Law and Policy Vol 6:90-110):

Level I : All homes that participated in Level I were occupied when the study began

Level II: Half of the homes that participated in Level II were occupied when the study began. Families who moved into previously unoccupied Level II homes were invited to participate after they moved in.

Level III: The homes that participated in the Level III abatement were unoccupied at the beginning of the study. Level III abatement called for a greater degree of disturbance of lead paint and thus it was only safe for vacant housing. Families in Level III homes were invited to participate after they moved in.

Level IV: All homes that participated in Level IV were occupied when the study began

Level V: All homes that participated in Level IV were occupied when the study began

“The families that already occupied their homes at the beginning of the study were asked to leave the home for the day or two it took to have the interventions preformed by an experienced and state certified lead reduction contractor” (from Pollak J. Journal of Health Care Law and Policy Vol 6:90-110):

Consent: The consent forms are not publicly available; however, portions have been published in journal articles. The families were informed that they were living in homes that were not lead free:

“Lead poisoning in children is a problem in Baltimore City and other communities across the country. Lead in paint, house dust and outside soil are major sources of lead exposure for children. Children can also be exposed to lead in drinking water and other sources.”

The families were also told:

“We are now doing a study to learn about how well different practices work for reducing exposure to lead in paint and dust. We are asking you and over one hundred other families to allow us to test for lead in and around your homes up to 8 or 9 times over the next two years provided that your house qualifies for the full two years of study. Final eligibility will be determined after the initial testing of your home. We are also doing free blood-lead testing of children aged 6 months to 7 years, up to 8 or 9 times over the next two years. We would also like you to respond to a short questionnaire every 6 months. This study is not intended to monitor the effects of the repairs and is not intended to replace the regular medical care your family obtains.”

Compensation: All families participating in all five categories of homes in the study:

- received free periodic blood lead testing
- received free transportation to the KKI clinic to ensure that blood lead testing was done
- received free cleaning supplies for the properties and were encouraged to use them
- received small payments and tokens for their time doing interviews with researchers

- received results of lead dust and blood lead testing (lead dust levels were returned after aprox. 9 months and blood lead levels were immediately returned)
- received free lead-safety education

Grimes v. Kennedy Krieger Institute

Late 1980s –early 1990s: the Kennedy Krieger Institute (KKI) begins a study on safe and inexpensive ways to remove lead hazards from homes in Baltimore.

1992: CDC revised the level at which a child is considered to have lead poisoning from 25 micrograms/deciliter that was established in 1975 to 10 micrograms/deciliter.

2001: Two parents sued the investigators and KKI for negligence on behalf of their children. The lawsuit was based on the following three claims:

1. KKI knew about hazardous lead levels in the homes and did not warn families in a timely fashion.
2. KKI failed to inform parents about the risks to the study.
3. KKI failed to prevent the children in the study from lead exposure and thus either poisoned the children or put them at risk for lead poisoning.

In order for the parents to prove negligence, they had to prove that KKI had a *duty of care* towards the families. In addition, the families also had to show that there was harm that was foreseeable and the harm resulted from failing to fulfill duties of care. KKI felt they had no [legal] duty of care to the families and argued, “even if the children were

injured or exposed to risks...it was not their responsibility to protect the children in the study from unreasonable harm or delays in the complete and prompt reporting of potential hazards.” (Kopelman 2002)

2001: The trial court agreed with KKI and dismissed the case and concluded that an investigator has no duty of care toward human subjects.

2001: The parents appealed the decision and the Maryland Appeals Court reversed the trial court’s decision. “the court maintained that KKI owed a duty to ward the children’s families in a timely way or elevated levels of lead in their blood because a special relationship existed between investigators and these subjects; the danger to the children was foreseeable, existing federal regulations create such a duty, and finally, that this consent form created a contractual duty.” (Kopelman 2002)

2001: The Maryland Appeals Court returned the case to the trial court and the case was settled out of court.

1. Discussion questions

1. What are the investigator's responsibilities to the children and families?
2. Can parents consent to their child participating in a non-therapeutic research study that may carry with it some risk to the child?
3. What is the acceptable level of risk for non-therapeutic pediatric studies for young children?

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